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ORIGINAL PAPER

An epidemiologic and clinical overview of medical and psychopathological comorbidities in major psychoses

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Abstract The presence of comorbidity in major psychoses (e.g., schizophrenia and psychotic subtypes of bipolar disorder and major depressive disorder) seems to be the rule rather than the exception in both DSM-IV and ICD-10. Examining comorbidity in major psychoses, however, requires an investigation into the different levels of comorbidity (either full-blown and subsyndromal) which should be analyzed in both psychopathological and medical fields. On one hand, the high prevalence of psychiatric comorbidity in major psychoses may be the result of the current nosographic systems. On the other hand, it may stem from a common neurobiological substrate. In fact, comorbid psychopathological conditions may share a biological vulnerability, given that dysfunction in specific brain areas may be responsible for different symptoms and syndromes. The high rates of comorbidity in major psychoses require targeted pharmacological treatments in order to effectively act on both the primary diagnosis and comorbid conditions. Nevertheless, few controlled trials in comorbid major psychoses had been carried out and treatment recommendations in this field have mostly an empirical basis. The aim of the present article is to provide a comprehensive and updated overview in relation to epidemiological and clinical issues of comorbidity in major psychoses.

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Abbreviations

MPs	Major psychoses
SUD	Substance use disorder
SK	Schizophrenia
BD	Bipolar disorder
pMDD	Psychotic major depressive disorder
OCD	Obsessive compulsive disorder
PTSD	Post-traumatic stress disorder
SP	Social phobia
PD	Panic disorder
GAD	Generalized anxiety disorder

Introduction

The concept of psychosis and major psychoses: historical and phenomenological aspects

Psychosis means literally a disorder of the psyche [1], and its nature has been debated for several decades. Originally, the term was introduced by Canstatt in 1841, emphasizing the psychic manifestation of a disease of the brain [2]. In 1845, Feuchtersleben, using the term "psychosis" as a synonym for psychopathy and stressing both the change in the entire personality and the interaction between physical and mental processes identified 4 main categories of psychosis: melancholia, mania, dementia, and idiocy [3]. Subsequently, the diagnostic criteria for psychosis shifted from the severity of the clinical manifestations and the

degree of impairment in social functioning to the presence of one or more core psychopathological symptoms including hallucinations, formal thought disorder, delusions, avolition/apathy, disorganized behavior, catatonic motor behavior, and depersonalization/derealization. In the 1850s, Morel developed his theory of "degeneration", regarding mental problems that take place from early life to adulthood, which also constitutes the first genetic theory of mental disorders based on the assumption that psychosis is the result of an innate biological defect, which becomes manifest in increasingly severe mental syndromes in lineal descents. Toward the end of the nineteenth century, Morel's theory was replaced by Moebius' endogeny theory that implied only a "constitutionally determined predisposition" for developing psychosis [2, 3]. Moebius, in addition, distinguished between exogenous and endogenous psychoses, using the former term to characterize the causation of mental disease through any extraneous influence and the latter to a hereditary degenerative cause. Fuerstner in 1881 and, subsequently, Bumke in 1920 distinguished organic and functional psychosis, being the former caused by structural defects or physiologic dysfunction of the brain, while the latter by unknown causes. Freud originally distinguished between neurosis and psychosis in the following way: "in neurosis the ego suppresses part of the id out of allegiance to reality, whereas in psychosis it lets itself be carried away by the id and detached from a part of reality". Unlike the neurotic, the psychotic subject does not "criticize" the disorders of his or her thoughts. Kraepelin adopted the terms psychosis (infection psychoses, exhaustion psychoses, intoxication psychoses, thyrogenous psychoses, and involution psychoses) in the 6th edition of his textbook of psychiatry, and he also identified, as major psychoses, dementia praecox and manic depressive insanity. In spite of its frequent use, however, the term "psychosis" remained vaguely defined until Jaspers defined it as a disease that "seizes upon the individual as a whole, regardless whether it is a hereditary disorder beginning at a certain time of life, or a non-hereditary disorder, which is called into being by an exogenous lesion." Adopting Jaspers' conceptual framework, Schneider defined psychoses as diseases with psychic symptomatology and somatic etiology [4].

After the introduction of the modern nosographic systems in Europe (the International Classification of Disease, "ICD", by the World Health Organization) and United States (Diagnostic and Statistical Manual of Mental Disorders, DSM, by the American Psychiatric Association), in 1980, the APA made sweeping changes in its classificatory system for mental disorders, and the opposition of Freudian matrix between neurosis and psychosis became obsolete. Both systems adopted a categorical approach that subdivided mental disorders into distinct sections (e.g., psychotic disorders, mood disorders, anxiety disorders) by means of diagnostic criteria.

Current classification of major psychoses and dimensional models

The categorical approach of modern classification systems represented an important step forward in the reliability and accuracy of psychiatric diagnoses despite robust criticism by authors who propose a dimensional approach to mental disorders. In addition, the classification of different new disorders coupled with the absence of a hierarchical diagnostic perspective allowed to diagnose multiple concomitant disorders, increasing, therefore, the presence of comorbidity. In fact, some authors consider the classification of DSM-III as the rise of the neo-Kraepelinian nosology with potential concerns regarding overdiagnosis of psychiatric syndromes ("nosologomania") [5]. On the other hand, a dimensional approach that takes into account specific psychopathological dimensions across different disorders would probably better capture the entire complexity of each condition, including not only Axis I features but also Axis II aspects along with temperamental characteristics, prodromic and residual symptoms [6]. As a matter of fact, if we focus on the psychotic dimension from a mere symptom perspective, considering as core symptoms the presence of hallucinations, delusions, lack of insight, and losing touch with reality [7], we recognize that not only traditional psychotic disorders such as schizophrenia and schizoaffective disorder present this dimension. In fact, other conditions may show psychotic features in some phases of the illness as well (e.g., mood disorders, substance use disorders, personality disorders). This dimensional model as opposed to the categorical approach has been conceptualized in different models like the spectrum model. In a dimensional perspective, to date, different conditions have been included within major psychoses such as SK, BD, and pMDD, each belonging to distinct DSM categories, with the presence of psychotic symptoms representing a *trait d'union* among them. In recent years, some authors have argued for a degree of continuity between SK and BD in opposition to the original Kraepelinian dichotomy [8–10]. SK, BD, and MDD are not seen as distinct disorders [11] as their symptoms overlap with each other, with intermediate conditions presenting psychotic, depressive, and manic features. In addition, they share underlying genetic risk factors to an increasingly recognized degree [12–15]. The psychotic spectrum can be considered as a highly convergent set of conditions, with strong genetic, epigenetic, and environmental heterogeneity yielding a relatively limited range of phenotypes [16–18]. In addition, growing evidence of an etiologic overlap between SK and BD has been suggested, showing common

risk factors between both conditions. These in turn suggest a genetic and environmental shared pathway with common neurobiological dysfunctions [19]. A recent meta-analysis reviewed family studies of probands with SK and BD reporting for the first time direct evidence for familial co-aggregation of these disorders [20]. Furthermore, 5 chromosomal regions that might be related to both bipolar psychosis and SK have been identified, suggesting that there might be "psychosis susceptibility genes" [21]. As regard to genome-wide association studies, recently, the international SK consortium has supported the polygenic basis of SK, partially shared with BD [22], and similar results have been reported by Moskvina and co-authors [23]. In contrast, an original article by Grozeva and colleagues reported a significant difference between BD and SK patients with respect to the global burden of copy number variants [24].

The link between major psychoses, nosographic systems, and comorbidity

The high rates of comorbidity in MPs represent another piece of evidence for the existence of a "continuum". The frequent observation of comorbidity in MPs may be partially seen as the product of current nosographic systems, but also in terms of a shared biological susceptibility. Comorbidity refers to the occurrence of two distinct syndromes in the same patient. Defined literally, every pair of syndromes, where the diagnosis of one does not categorically exclude the diagnosis of the other, is potentially comorbid [25]. In particular, clinical comorbidity is defined as one disorder influencing the course, outcome, and treatment response of a second coexisting disorder [26]. Different types of comorbidity have been detected: true (involving clinical distinct disorders) and artifactual (a by-product of DSM/ICD strategy to split into categorical diagnoses) [27]. Furthermore, comorbidity can be detected at different levels as syndromal (full-blown, distinct disorders), sub-syndromal (as subthreshold, subclinical comorbidity), and dimensional (including, besides core features, prodromal and residual symptoms and Axis II features) [27]. Given that comorbidity is so common within MPs for different reasons (e.g., nosographic, biological) and that its presence may complicate the detection, presentation, and outcome of MPs [6], surprisingly, only in the last decade, there has been a systematic recognition of the phenomenon, even though in the majority of clinical studies—particularly treatment trials—comorbidity has been traditionally considered an exclusion criterion. In addition, it is noteworthy to highlight that MPs may be comorbid not only with other psychiatric conditions but also with other medical conditions. Different reasons for the high rate of comorbidity between MPs and medical comorbidity have also been put forward.

In order to approach the complex phenomenon of comorbidity within MPs, the aim of the present article was to provide a comprehensive overview of main comorbidity patterns in these conditions in both medical and psychopathological fields, with specific emphasis on epidemiologic, clinical, and treatment issues.

Methods

We reviewed published data on comorbidity in MPs searching on Medline and Cochrane Library up to July 2010 and using the following keywords: "comorbidity," "major psychoses," "schizophrenia," "bipolar disorder," and "psychotic major depressive disorder". Literature search for this narrative review was conducted by three independent reviewers (M.S., A.A., R.A.P.). Publication search included meta-analyses, randomized clinical trials, naturalistic and retrospective studies, and clinical reviews. Furthermore, a hand-search for relevant articles was conducted examining references of retrieved publications. In particular, we were interested in analyzing comorbidity patterns for each disease—both medical and psychiatric—in terms of epidemiology, providing possible theories and explanations in this regard. We then focused on clinical impact of comorbidity in MPs in terms of outcome. Finally, we reviewed pharmacological treatment options in comorbid MPs on the basis of the literature and published guidelines.

Results

Taken as a whole, the Medline search identified 2,225 publications. However, only 226 articles were included in the present overview. The failure to specifically focus on comorbidity patterns in the majority of the studies dealing with MPs was the most common reason for exclusion.

Schizophrenia

Medical comorbidity

Epidemiology of medical comorbidity SK represents per se a major risk factor for a wide variety of medical conditions, and it has been estimated that more than 50% of patients with SK have a medical diagnosis, being their overall mortality twice the general population [28, 29]. Carney et al. [30] reported that 33% of schizophrenics with a mean of 40 years had three or more medical comorbidities. Despite the high rates of medical comorbidity,

schizophrenic patients less frequently receive a medical diagnosis compared with the general population. Many medical illnesses, in fact, are often misdiagnosed or underdiagnosed causing prolonged hospitalizations and treatment failure [31]. Laursen and co-workers [32] compared mortality rates among severe mental disorders, finding that patients with SK had higher mortality from natural causes compared with both unipolar and bipolar depressed subjects. As a matter of fact, it seems that over the last decade the improvement in health service allowed the reduction in mortality rates in general population with the exception of patients with SK whose mortality rates did not significantly change [33].

Medical comorbid conditions Several studies show an increased prevalence of infections, cardiovascular diseases, obstetric complications, respiratory, endocrinologic, and metabolic disorders in schizophrenic patients (see Table 1). Human immunodeficiency virus, hepatitis, and infections linked to substance abuse and sexual risk behaviors are a major concern with these patients, as well as treatment-related side effects [34, 35]. Poor dental status can be the source of infections and endocarditis—problems quite common in schizophrenics, especially in developing countries [30, 36].

The prevalence of cardiovascular risk is particularly high in patients with SK. A large study showed that 83% of schizophrenic patients had at least one chronic medical illness, hypertension being the most common. The prevalence of hypertension, chronic obstructive pulmonary disease, and coronary artery disease was more than double compared to patients with other primary diagnoses [37]. In addition, it has been estimated that schizophrenics are 3 times as likely to experience sudden deaths than the general population, and this increased risk might be attributed to an intrinsic variability of QT time plus autonomic dysfunction that lead to malignant arrhythmias [38]. Recently, Laursen and co-workers found that individuals with severe mental disorders had a high mortality rate from heart disease, being that of schizophrenics higher than bipolar patients, with a lower fraction of patients undergoing somatic care and invasive cardiac procedures, with consequent suboptimal care [39].

Among endocrine conditions present in subjects with SK, thyroid dysfunction [40], in particular acquired hypothyroidism, has been found to be nearly 3 times more prevalent among patients discharged with a primary diagnosis of SK compared with non-schizophrenic patients [37]. In a retrospective study, hyperprolactinemia, particularly frequent in patients receiving first-generation antipsychotics as well as risperidone and paliperidone [41], showed an increased risk too.

Diabetes, obesity, and metabolic syndrome are strongly linked to lifestyle. Nevertheless, a study on psychotic subjects reported that first-episode, drug-naive patients with SK have impaired fasting glucose tolerance, more insulin resistance, higher levels of plasma glucose, insulin, and cortisol compared with age- and sex-matched healthy subjects, supporting the hypothesis of a primary altered glucose metabolism in SK [42] as well as an increased predisposition toward metabolic dysfunction independent of environmental exposure [43]. There is also a possibility that a shared genetic susceptibility characterizes both diabetes and SK, as indicated by family studies (with limited sample sizes) suggesting that first-degree relatives of patients with SK have a higher prevalence of type 2 diabetes than expected. These findings allowed authors to hypothesize that these 2 diseases might share a common pathophysiological background involving the regulation of mitochondrial oxidative energy metabolism [44]. A cross-sectional study investigating the prevalence of metabolic syndrome (MS) in SK in general population found that one-third of the cohort presented MS, in particular within the 20–29 age group. Furthermore, patients with MS had a higher age- and sex-corrected 10-year risk of coronary heart disease (CHD) event [45].

Epilepsy was found to be twice as prevalent at discharge in patients with SK compared with patients discharged with other primary diagnoses [37]. This association has no clear pathogenic mechanism identified and has been reported in previous studies [46].

Other connections between SK and somatic symptoms, though at a lower level, include musculoskeletal disease with significant osteoporosis rates, probably secondary to increased prolactin levels in patients taking long-term antipsychotic therapy [47]. On the other hand, an inverse

Table 1 Epidemiological estimates of some comorbid medical diseases in SK

Medical diseases	References	Prevalence in SK	Prevalence in general population [224]
Diabetes mellitus	Weber et al. [37]	8.4% (cross-sectional)	3.4% (lifetime)
Impaired fasting glucose tolerance	Ryan et al. [42]	15.4% (cross-sectional)	–
Metabolic syndrome	Meyer and Stahl [43]	11.9–66.7% (range of 11 previous studies)	25% (lifetime)
Asthma	Weber et al. [37]	4.2% (cross-sectional)	10% (lifetime)
Hypertension	Weber et al. [37]	14% (cross-sectional)	20% (lifetime)

correlation between SK and rheumatoid arthritis has been reported [48], whereas a possible link between SK and cancer is still debated. As results from a prospective study on a cohort of schizophrenic patients, accidents and traumatic injuries seem to be important causes for the excess mortality in SK [49]. Finally, mothers with SK have been shown to present multiple obstetric complications with increased risk of stillbirth and neonatal death compared to general population potentially due to substance and alcohol abuse and antipsychotics intake [50].

Possible determinants of medical comorbidity High medical morbidity and mortality in SK may be attributed to an unhealthy lifestyle, possibly secondary to a low level of education and poor social functioning. Interventions aimed to decrease lifestyle risk factors and to improve care availability may be critically important in reducing morbidity and mortality in these patients [37, 51]. Furthermore, it is important to recognize that poor physical health occurs at an early age in schizophrenic patients. Cognitive and behavioral impairments, adverse effects of medications used in the treatment of SK, delay in seeking care, comorbidity with substance and alcohol abuse, and poor adherence to medical treatment advices may also increase the risk of medical comorbidity [46, 52, 53]. High rates of cigarette smoking, lack of exercises, poor diet, and alcohol abuse can also lead to cardiovascular disorders. Psychotropic drugs used in the treatment of SK may have different cardiac side effects: typical antipsychotics have high risk of arrhythmias and atypical antipsychotics are associated with metabolic side effects that may increase cardiovascular risk [54]. Other treatment-related side effects in schizophrenics are hyperpigmentation or cataracts, an increase in prolactin levels leading to galactorrhea, sexual dysfunctions, amenorrhea, with potential long-term consequences such as osteopenia and osteoporosis and an enhanced risk of fractures [55]. Neurological impairment (e.g., dystonia, akathisia, parkinsonism, dyskinesia, neuroleptic malignant syndrome) caused by typical antipsychotics is also frequent with a greater risk in older patients, at an early stage of treatment and an annual incidence of extrapyramidal side effects of 3–5% [56, 57].

Psychopathological comorbidity

Epidemiology of psychopathological comorbidity Recent studies suggest that the rate of psychopathological comorbidity in SK is high [58, 59] (Table 2). In particular, anxiety, depressive, and substance abuse disorders are the most common comorbid conditions. Substance abuse disorders (SUDs) are extremely common in schizophrenic patients with a lifetime prevalence up to 65% [60, 61]. Most commonly abused substances are nicotine, alcohol, cocaine, and cannabis [62] with an increasing risk of violent crime (4–6 times the level of general population) [63]. Commonly recognized risk factors for comorbid SUD are being men, unmarried, and having a low education level [64].

With respect to lifetime rates of comorbid anxiety disorders, panic disorder (PD) is present in 15% of patients with SK and is more common in the paranoid subtype [59]. Post-traumatic stress disorder (PTSD) has a prevalence of 29% in schizophrenics compared with general population and has been associated with more severe symptoms. Obsessive compulsive disorder (OCD) is comorbid in 23% of schizophrenics and some authors have suggested that the co-occurrence of SK and OCD may represent a specific schizo-obsessive phenotype of SK [65]. The prevalence of OC symptoms (10–64%) and of OCD (31.7%) varies widely across studies and may be overestimated due to

Table 2 Epidemiological estimates of main comorbid psychopathological conditions in SK

Psychiatric disorders	References	Prevalence in SK	Prevalence in general population [225, 226]
Anxiety disorders			
GAD	Tibbo et al. [70]	26.7% (cross-sectional)	1.7% (12 month)
OCD	Buckley et al. [59]	23% (lifetime)	0.7% (12 month)
PTSD	Buckley et al. [59]	29% (lifetime)	6.8% (lifetime)
	Tibbo et al. [70]	0% (cross-sectional)	
PD	Buckley et al. [59]	15% (lifetime)	1.8% (12 month)
	Tibbo et al. [70]	6.6% (cross-sectional)	
SP	Tibbo et al. [70]	11% (cross-sectional)	2.3% (12 month)
Substance abuse disorders	Cantor-Graae et al. [60]	48.3% (lifetime)	3.4% (12 month)
	Buckley et al. [59]	47% (lifetime)	
Depressive symptoms	An der Heiden [68]	50% (cross-sectional)	–
		30–35% (month-prevalence)	
Major depression	Buckley et al. [59]	50% (lifetime)	16.6% (lifetime)

difficulties in clinically distinguishing between obsessions and delusions [66]. Social phobia (SP) is comorbid in the 11% of schizophrenics and affective disorders, particularly major depression in 50% of cases [59]. Many studies have investigated the prevalence of depression in SK, and it is important to remind that such studies have varied considerably in terms of definitions employed for SK and depression, observed interval, assessment, and patient status. Taken as a whole, such reasons might in part explain the significant variation of prevalence reported ranging from 7 to 75% [67]. The prevalence of depression had been studied prospectively over 12 years after first hospital admission in a sample of 107 patients in the ABC SK study, finding that depressive symptoms are particularly frequent during a psychotic episode at a rate of approximately 50% [68]. Of note, a cross-sectional study by Birchwood and colleagues [69] reported the prevalence of depression in schizophrenics to be around 29%.

Psychopathological comorbid conditions and clinical aspects The presence of comorbid anxiety disorders in SK has been studied by Tibbo and colleagues who found different rates ranging from 0% (PTSD) to 26.7% (GAD and agoraphobia without panic) in a cohort of patients with SK [70]. However, such rates decreased when authors controlled for anxiety symptoms secondary to delusions and hallucinations, being comorbid anxiety disorders in SK partially related to psychotic symptoms.

With respect to comorbid PTSD, it seems that such comorbidity—when present—would imply more severe cognitive impairment and poor neurocognitive outcome, already associated with chronic SK [71]. With regard to OC spectrum comorbidity, a recent meta-analysis showed that the presence of OC symptoms is significantly associated with greater severity of positive and negative psychotic symptoms [72]. OC symptoms may be present throughout the entire course of SK and may be prodromal to psychotic symptoms. In some studies, moreover, OC symptoms have been associated with an earlier age at onset of SK [73].

SP may be particularly important to diagnose and manage among patients with SK. In a study with 117 schizophrenics, 11% of the sample was diagnosed with comorbid SP showing higher PANSS severity and avoidance scores [74].

With respect to comorbidity with SUD, cannabis use is considered a contributory cause of SK and development of psychotic illness. However, only a small proportion of cannabis users develop psychosis. This can be partly explained not only by the amount and duration of cannabis consumption and by its strength but also by the age at which individuals are first exposed to cannabis. Genetic factors, in particular, are likely to play a role in the short- and the long-term effects cannabis may have on psychosis outcome. Multiple variations within multiple genes rather than single genetic polymorphisms along with other environmental factors may interact with cannabis to increase the risk of psychosis [75]. Interestingly, a recent magnetic resonance imaging study concluded that the loss of gray matter, commonly seen in the brains of schizophrenic patients, proceeds nearly twice as fast in patients with cannabis abuse over a 5-year follow-up, adding new evidence in favor of a detrimental effect of cannabis in SK [76]. Factors influencing SUD risk in SK may be more numerous and complex than those modulating SUD risk alone in general population. On the one hand, SK could be a biological predisposition to substance abuse by altering the brain reward system. On the other hand, increased vulnerability to addictive behaviors may reflect the impact of the neuropathology of SK on the neural circuitry mediating drug reward and reinforcement [66]. In a recent study, it has been shown that abnormalities in the hippocampal formation and frontal cortex facilitate the positive reinforcing effects of drug reward and reduce inhibitory control over drug seeking behavior. Disturbances in drug reward are partly mediated by dysregulated neural integration of dopamine and glutamate signaling in the nucleus accumbens resulting from cortical and hippocampal dysfunction [77]. Patients with comorbid alcohol and substance abuse showed a higher rate of relapse compared with non-abusers. Comorbid antisocial personality disorder and former involvement in criminal acts were predictors of violence in schizophrenic people living in the community [78].

In general, patients with SK are at increased risk of developing lifetime major depression, particularly in the acute and post-psychotic phase [37]. Depression may be seen as a core syndrome in SK preceding, coming along with or following psychotic episode [68, 79]. In particular, the onset of SK has been reported to be frequently marked by depressive symptoms, followed by negative symptoms and functional impairment. This prodromal core syndrome became more prevalent as the disorder progressed, reappearing in psychotic relapses, as also An der Heiden and colleagues reported [68].

Furthermore, depression in SK may be a response to psychological deficits [69]; a cross-sectional study by Sim and co-workers evaluated subjects with a first-episode SK and comorbid depressive syndrome, showing that such patients present a greater awareness of their mental illness and its social consequences but a poorer overall quality of life compared with first-episode SK patients without depression [80]. Depression could also be a side effect of pharmacological therapy [81], a consequence of alcohol, drug abuse [82], or other organic diseases in many ways [79].

From a nosographic perspective, major depression in the context of SK may be paradigmatic of the difference between comorbidity and co-occurrence: it may be, in fact, viewed as a dimension of SK or as a distinct condition [83, 84]. In any case, depressive comorbidity is a major concern in SK enhancing suicidal behaviors. Several studies have suggested that negative symptoms are correlated with suicidal risk in schizophrenics [85]. The link between anhedonia and a high risk of suicide in schizophrenics suggests that this symptom could be more closely related to depression than to negative symptoms. We can assume that suicidal behavior can result from both positive and depressive symptoms. Notably, the most common correlates of suicidality in SK are depressive symptoms and the depressive syndrome, although severe psychotic and panic-like symptoms may contribute to suicidality [86].

Possible determinants of psychopathological comorbidity and treatment issues Despite its importance, research on the treatment of comorbidity in SK has been limited. Most recent pharmacological approaches to SK are supposed to take into account the different clinical dimensions of the disorder. Treatments may require a combination of antipsychotics, antidepressants, mood stabilizer, and anxiolytic compounds, although few studies have found this helpful. Such a wide spectrum of action is in part characteristic of atypical antipsychotic compounds that have a high ratio of serotonin receptor 5HT 2A/dopamine receptor D2 antagonism, a high ratio of noradrenaline receptor/D2 receptor antagonism, preferential mesolimbic binding, and fast dissociation from the D2 receptor [87–89]. Furthermore, atypical antipsychotics seem to be useful for the depressive symptoms of SK, including those associated with a greater risk for suicidality or unfavorable disease course. Novel antipsychotics, in fact, are of great importance in this context as they are more efficacious than neuroleptics in treating depressive symptoms [83]. Nevertheless, the new compounds are associated with substantial weight gain, as well as with adiposity-dependent and possible adiposity-independent changes in insulin sensitivity and lipid metabolism, which increases the risk of diabetes and cardiovascular disease [90]. Clozapine and olanzapine treatment are associated with the highest risk in this perspective. Risperidone, quetiapine, amisulpride, and zotepine generally show low to moderate levels of mean weight gain and a modest risk of clinically significant increases in weight. ziprasidone and aripiprazole are generally associated with minimal mean weight gain [91].

With respect to the treatment of comorbid SK and the use of augmentative compounds (e.g., mood stabilizers), the efficacy and tolerability of lamotrigine in 5 patients with SK and 6 patients with schizoaffective disorder with comorbid OC symptoms was evaluated in an 8-week, open-label trial during which lamotrigine was added to ongoing treatment. The Y-BOCS score for the 9 completers decreased significantly from baseline to week 8. Five patients, all with schizoaffective disorder, were considered responders. Depressive symptoms, assessed with the Calgary Depression Rating Scale, improved significantly, and this change positively correlated with OC symptom improvement [73]. In another recent study, patients with comorbid SK and OC symptoms treated with aripiprazole monotherapy have shown a modest improvement on the YBOCS, CGI, and PANSS scores [92].

Comorbidity between SK and SUD is often associated with prominent positive symptoms and a drastic reduction in treatment compliance and leads to poorer outcome complicating the treatment of both conditions. Some substances, moreover, can interfere with antipsychotic metabolism, either worsening side effects and therapeutic outcome. Finally, drug abuse decreases treatment compliance leading to a worse outcome with higher relapse and suicide rates [93]. The "self-medication hypothesis" suggests that smoking may alleviate some of the cognitive deficits commonly experienced by schizophrenics. Substances, moreover, might enhance the mesocorticolimbic pathway improving the detection of dopamine in these neurons [94]. Chronic hyperactivation of the neuromodulatory system, as occurring in drug addiction, results in a persistent neuroadaptation of the dopaminergic pathway [95]. As for other drugs, it is possible that schizophrenic patients abuse marijuana not only for its hedonic properties but also for other psychotropic effects of cannabinoids involving the endocannabinoid system [96]. A recent review stressed the use of atypical antipsychotics in SK with comorbid SUD: the atypicals, in fact, seem to be effective in treating psychotic patients with and without comorbid substance abuse. Several studies, moreover, indicated that atypical compounds, clozapine in particular, have shown efficacy in treating psychotic symptoms and in reducing craving and substance addiction [61]. Recent studies also recommend the use of depot formulation of antipsychotics due to the high probability of non-adherence in patients with dual diagnosis [97]. A recent study focused on the alterations of the endocannabinoid system in schizophrenics reported anandamide, an endogenous CB(1) receptor agonist, as a promising target for medications to reduce substance abuse in these patients [98]. Among atypicals, moreover, risperidone and particularly clozapine have shown a specific efficacy over hostile and aggressive behaviors in SK, a characteristic that was also reported with anticonvulsants, lithium and high-dose beta-blockers (e.g., propranolol, pindolol) according to international treatment guidelines [99, 100]. In the treatment of agitation, olanzapine showed a good efficacy and tolerability including reduced use of additional benzodiazepines, anticholinergic

drugs and less dystonia, and EPS compared with other antipsychotics [101].

The use of antidepressants in SK is controversial, and currently, their use in association with antipsychotics is indicated when depressive symptoms meet the syndromal criteria for major depression or are very severe, cause significant distress (e.g., when accompanied by suicidal ideation) and/or interfere with patient' functioning [99]. Beyond tricyclic antidepressants, SSRIs and dual reuptake inhibitors have been found to be useful in the treatment of depression in SK; however, it is important to take into account the possible pharmacokinetic interactions with certain antipsychotic medications [67].

Treatment decisions should incorporate information about medical risk factors such as cardiovascular risk, metabolic and endocrine side effects of antipsychotics in order to prevent or minimize them and improve patient' compliance and quality of life [102]. Recently, a French group [103] developed specific guidelines recommending the detection of medical illness at the first time of an episode of mental illness. The management of medical comorbidity should be shared with other specialists.

Bipolar disorder

Medical comorbidity

Epidemiology of medical comorbidity Patients with BD have healthcare costs that are as much as 4 times greater than costs for patients without mental disorders. They have extensive psychotropic medication use. A consistent part of these costs is driven by medical illness [104–106]. A cross-sectional study by Fenn and co-workers [107] reported that most multiple-episode bipolar patients presented a medical comorbid condition at the time of psychiatric hospitalization. More recently, a retrospective study reported the presence of multiple comorbid medical conditions ($\geq$3) in more than 40% of individuals with BD compared with controls [108]. Medical comorbidity has been reported to be more common in women than men, in particular thyroid disease, migraine, and obesity [109].

The prevalence of medical comorbidities as well as their effect on clinician's assessment of disease severity and time to improvement was assessed, retrospectively, in a large outpatient sample of 1,379 bipolar patients. Most prevalent systemic illnesses were endocrine and metabolic disorders (13.6%), diseases of the circulatory system (13.0%), and diseases of the nervous system and sense organs (10.7%). Specifically, the most frequent ones were cardiovascular diseases/hypertension (10.7%), chronic obstructive pulmonary disease (COPD), asthma (6.1%), diabetes (4.3%), HIV infection (2.8%), and hepatitis C infection (1.9%). As expected, medical comorbidities increased with age and the prevalence of comorbidity was influenced by the duration of untreated illness [110, 111]. Recently, in an extensive prospective metabolic study, Van Winkel and colleagues reported a high prevalence of diabetes (6.7%) and pre-diabetic abnormalities in a sample of 60 BD patients [112].

A recent study with 98 adult bipolar outpatients with co-occurring SUD investigated prospectively the relationship between phenomenology, response to mood stabilizers, and medical comorbidity [113], finding that all patients had at least 1 medical illness (most frequently of respiratory kind, 72%). The presence of high medical burden, observed in 64% of the sample, along with a history of suicide attempts and physical abuse as well as advanced age, was associated with a diagnosis of BD I.

Cardio- and cerebrovascular diseases seem to occur at twice the rate of the general population in BD, and higher rates of mortality and morbidity for cardiovascular diseases have been reported in BD compared with unipolar depression as reported in a sample of hospitalized affective disordered patients followed prospectively for 22 years or more [114].

Medical comorbid conditions Among cardiometabolic conditions comorbid with BD, diabetes, cardiovascular disease and dyslipidemia seem to be the most frequent [115, 116] (Table 3).

The prevalence of diabetes in BD seems to be 3 times greater than in the general population as reported in a review by McIntyre [117]. Furthermore, the same group [116] reported abnormal lipid values in BD patients, with an increased prevalence of metabolic syndrome compared with general population. Neurological, respiratory, and infectious diseases are also prevalent in bipolar patients [116]. Migraine, in particular, is two times more frequent in bipolar II patients, particularly among subjects with comorbid anxiety disorders compared with general population [118, 119]. For unknown reasons, multiple sclerosis is the most consistently comorbid condition in BD, occurring at twice the expected rate compared with general population [120, 121]. Furthermore, bipolar symptoms may precede other neurological signs of multiple sclerosis or may occur in the context of relapses or exacerbations [122, 123].

BD has also been associated with obesity, MS, high rates of smoking, and poor health-related behaviors [124–126]. In addition to pharmacological treatment—which may per se influence the vulnerability to MS—risk factors for weight gain and obesity in patients with BD include comorbid binge eating disorder, the lifetime number of depressive episodes, excessive carbohydrate consumption, and low rates of physical exercise. Obesity, in particular, has been correlated with a poorer outcome in patients with

Table 3 Epidemiological estimates of some comorbid medical diseases in BD

Medical diseases	References	Prevalence in BD	Prevalence in general population [224]
Diabetes	Beyer et al. [110]	4.3% (cross-sectional)	3.4% (lifetime)
	Van Winkel et al. [112]	6.7% (cross-sectional)	
Pre-diabetic abnormalities	Van Winkel et al. [112]	23.3% (cross-sectional)	5% (lifetime)
Obesity	McElroy et al. [124]	21% (cross-sectional)	20% (lifetime)
COPD/asthma	Beyer et al. [110]	6.1% (cross-sectional)	10% (lifetime)
Migraine	McIntyre et al. [119]	24.8% (cross-sectional)	40% (lifetime)
HIV infection	Beyer et al. [110]	2.8% (cross-sectional)	1% (lifetime)
Hepatitis C infection	Beyer et al. [110]	1.9% (cross-sectional)	1.8% (lifetime)

BD I. In fact, obese bipolar patients tend to present a higher lifetime number of depressive and manic episodes, more severe and difficult-to-treat episodes than the non-obese patients. Furthermore, obesity can contribute to sleep apnea, disrupting circadian rhythms and thus causing mood destabilization [127]. Compared with general population, the prevalence of MS was found to be significantly higher in patients with BD [128, 129]. Such condition was mainly due to a higher prevalence of obesity, high triglyceride levels, and low HDL cholesterol levels.

Patients with BD are at increased risk of developing dementia and the risk grows with increasing number of episodes [130, 131]. In addition, an elevated cancer risk in patients with BD has been reported in both men and women [132]. Fibromyalgia has also been highly associated with BD, suggesting that these conditions may share pathophysiological alterations [133].

Possible determinants of medical comorbidity Despite the association among mental disorders like BD and physical health complications, medical conditions remain frequently under-recognized and undertreated in clinical practice. In fact, the life expectancy for patients with severe mental illnesses like BD is approximately 30% lower than general population [134]. Several factors contribute to this gap including cognitive impairment of patients, reduced ability to function, lack of communication skills in addition to a possible genetic susceptibility that increases the likelihood of a comorbid physical condition and premature death [134]. From a neurobiological prospective, emerging evidence suggests that specific comorbid medical conditions, such as diabetes, may be underpinned in bipolar individuals by overlapping neurobiological networks. Disturbances in glucocorticoid/insulin signaling and immunoinflammatory effector systems are points of pathophysiological commonality between BD and "stress-sensitive" medical disorders. Even though etiopathogenetic mechanisms of this observed comorbidity are unclear, hypotheses including genetic and neuroendocrinological acquisitions (according to which hypercortisolemia induces diabetes and diabetic vascular lesions contribute to mania) as well as psychopharmacological contributions have been proposed and associated with weight gain. Recently, Soreca and colleagues [135] hypothesized that the physiopathology of BD may in turn facilitate the development of certain specific medical conditions that would consequently represent a complication, if not a core feature, of the mental disorder rather than an incidental event or a treatment-related side effect.

Recently, a review by Roshanaei and colleagues [136] confirmed that cardiovascular disorder appear to be the most consistent cause of premature mortality in BD, identifying in unhealthy lifestyle, biological factors, adverse pharmacological effects, and disparities in health care, the possible causes for such higher mortality.

Losing weight is a challenge, particularly for patients with severe mental illness; thus, diet and exercise counseling should be provided to all bipolar patients, perhaps in association with behavioral therapy [137]. Furthermore, obesity has negative psychosocial consequences such as stigmatization in everyday life, a negative impact in general physical and psychological well-being and functioning. Recently, McIntyre [137] in the UNITE global survey found that weight gain was the most cited adverse event associated with medication use. Moreover, it was confirmed as a contributing factor to general medical comorbidity (such as diabetes) and as a detractor to quality of life.

Psychopathological comorbidity

Epidemiology of psychopathological comorbidity Psychopathological comorbidity is the rule rather than the exception in BD given that more than 60% of patients have comorbid diagnosis [138] (Table 4). Lifetime prevalence of comorbidity is high in BD patients with an increased risk in women [139]. The prevalence of the comorbid conditions varies by gender. Women present more frequently anxiety disorders [98] and eating disorders, whereas men alcohol abuse and substances addiction [140]. Anxiety disorders and substance abuse disorders account for a large

Table 4 Epidemiological estimates of main comorbid psychopathological conditions in BD

Psychiatric disorders	References	Prevalence in BD	Prevalence in general population [225, 226]
Anxiety disorders (total)	Merikangas et al. [138]	74.9% (lifetime)	12% (12 month)
GAD	Merikangas et al. [138]	29.6% (lifetime)	1.7% (12 month)
OCD	Merikangas et al. [138]	13.6% (lifetime)	0.7% (12 month)
PTSD	Merikangas et al. [138]	24.2% (lifetime)	6.8% (lifetime)
PD	Merikangas et al. [138]	20.1% (lifetime)	1.8% (12 month)
SP	Merikangas et al. [138]	37.8% (lifetime)	2.3% (12 month)
Substance abuse disorders	Merikangas et al. [138]	42.3% (lifetime)	3.4% (12 month)
Personality disorders	Fan and Hassel [223]	12–89% (range of 32 previous studies)	–
Eating disorders	McElroy et al. [169]	9–18% (lifetime)	0.4% (12 month)

part of comorbidity, reaching up to 90% for anxiety disorders and 70% for substance abuse [26, 139, 141, 142]. The National Comorbidity Survey reported that the large majority of BD I patients (86.7–92%) had a coexisting anxiety disorder [138]. These include GAD, OCD, SP, PD, and PTSD [138, 143]. Anxiety disorders, alone or in association with mood disorders, are associated with a range of troublesome clinical issues including increased suicide risk, worse outcome [144], and psychosocial dysfunction [145].

Previously, Boylan and co-workers evaluated the rates of comorbid anxiety disorders in a sample of 138 outpatients with BD and found that over half (55.8%) had at least one anxiety disorder and nearly one-third (31.8%) had 2 or more comorbid anxiety disorders [146]. The most common anxiety disorder was GAD followed by PD.

With respect to comorbid PD, the Epidemiologic Catchment Area (ECA) study found that 21% of bipolar subjects had PD [147]. PD shows a close relationship with BD and both disorders seem to have a familial basis. In a study of 109 bipolar probands and 226 siblings, Doughty and colleagues [148] found that only affectively ill subjects, whether probands or siblings, had PD. None of the unaffected siblings of bipolar probands (i.e., siblings with no mood disorder) had full syndromal PD and only rarely (3.4% vs. 28% of bipolar I subjects) had occasional panic attacks. Therefore, PD seems to be associated mostly with affective disorder in families with a history of BD. Furthermore, PD was more common in BD than in MDD in these families [148]. Interestingly, analysis of diagnostic patterns in a family sample for a linkage study of BD confirmed the association between BD and PD [149]. In addition, the same group found a genetic predisposition for panic attacks in bipolar subjects specifically linked to chromosome 18 [150].

A converging biological substrate seems to link PD, BD, and suicidality. MacKinnon and Zamoiski [151] proposed that mood and anxiety disorders may share the same genotype or may have the same causal risk or common pathophysiological alterations. BD with psychiatric comorbidity seems to increase suicidality, as reported in several studies [152, 153]. A longer duration of untreated illness (DUI) had been linked to negative outcomes in BD and, in particular, to a higher number of suicide attempts and attempters/follow-up [154]. In addition, in the same study, a higher frequency of comorbidity with SUD and PD following the onset of BD was found in the subgroup with a longer DUI. This result is consistent with a recent study indicating that comorbidity with anxiety disorders and substance abuse is a risk factor for suicide attempts in BD [155].

In the ECA study, OCD was frequently comorbid in type I and II bipolar subjects (21% of the sample) [147]. This is nearly tenfold greater than the prevalence of OCD in the general population (2.6%). This finding was replicated in the National Comorbidity Survey Replication (lifetime comorbidity 16.6%) family members of bipolar I and II probands had a higher rate of OCD [156], which suggests a familial or genetic association. However, some researchers believe that OC symptoms, particularly when episodic, may actually represent a variation of how bipolar illness is expressed and not a true comorbidity [157].

Bipolar subjects may be at a higher risk of experiencing traumatic events. This may be due to problematic behavior during mania or due to increased childhood trauma [158]. Furthermore, traumatic events that occur during a manic or hypomanic episode have a high likelihood of subsequently inducing PTSD symptoms [159, 160]. PTSD is highly prevalent in the general population but may be more common in bipolar patients, ranging from 16 to 39% of bipolar I patients in the National Comorbidity Replication Study [138, 161]. Bipolar women (either I or II) are nearly twice as likely to have PTSD compared with men [162].

GAD occurred in nearly one-third of bipolar patients in the National Comorbidity Replication Study (29.6%), being more frequent in type I bipolar patients (38.7%) [138].

SP occurred in 4.7–5% of bipolar I subjects who participated in the National Comorbidity Survey and its

replication [138]. Additionally, the National Epidemiologic Survey on Alcohol and Related Conditions Study, which surveyed more than 40 thousand community adults, found a lifetime prevalence of social anxiety of 5%, being comorbidity in BDI particularly frequent [163].

With respect to geriatric patients with BD, in the Veterans Health Administration database, 29% of patients had comorbid SUD (8.9%), PTSD (5.4%), other anxiety disorders (9.7%), or dementia (4.5%) [164].

Psychopathological comorbid conditions and clinical aspects Coexisting anxiety disorders are associated with poor outcome in bipolar patients. Patients with comorbidity, in fact, have a greater symptom burden, poorer treatment response, more depressive complaints, lower quality of life, and more suicidal ideation. Even subsyndromal anxiety is associated with poorer outcome [165].

In 983 subjects studied in the STEP-BD study, an earlier age of onset of bipolar illness (most patients [70%] had BD I) was associated with higher rates of comorbidity of all anxiety disorders as well as substance abuse. Not surprisingly, earlier age at onset was also associated with poorer outcome, i.e., a higher number of recurrences, shorter periods of euthymia, and a greater likelihood of previous suicide attempts or violent behaviors.

Lee and co-workers [166] recently compared a sample of bipolar patients with or without comorbid anxiety disorders. On several measures, bipolar patients with comorbid anxiety disorders were more significantly ill than those without comorbid anxiety disorders. Patients with an anxiety disorder were more likely to have an earlier age of onset of illness, higher scores on the rating scales, and lower functioning. Comorbid anxiety disorders were also associated with a more frequent history of substance abuse and higher scores for suicidal ideation.

The clinical presentation of BD with comorbid SUD is characterized by more frequent mixed episodes and rapid cycling course, delayed time to achieve remission, more lifetime hospitalizations, earlier onset, and higher suicide risk [167]. Recently, Gao and co-workers compared the prevalence differences of anxiety disorders in rapid cycling BD I and II, finding that rapid cycling BD I patients with a history of substance use have an increased risk of GAD, PD but not OCD, whereas no differences were found between BD I and II without a history of substance use [168].

A study by McElroy and co-workers in a sample of BD patients found a high rate of comorbid lifetime Axis I disorders (65%) including anxiety disorders, SUDs, and eating disorders [26]. They found no difference between BD I and II patients. Both lifetime and current Axis I comorbidity were associated with an earlier age at onset of affective symptoms; in particular, current comorbidity was associated to cycle acceleration and more severe episodes over time. The same group analyzed the specific comorbidity between BD and eating disorders, including subthreshold and spectrum manifestations, reporting high rates of comorbidity for this specific association [169].

Angst and colleagues compared comorbidity rates between hypomania and binge eating disorder, finding higher rates in hypomanic patients than in healthy controls [170]. In particular, patients with brief recurrent hypomania presented more binge episodes than hypomanics (22% vs 13%). Lewinsohn and co-workers interestingly found that subthreshold BD was associated with both subclinical and full-blown eating disorders [171]. Taken as a whole, these data stress the importance of investigating the full spectrum of bipolar and eating disorders when examining comorbidity [169].

Prevalence data of Axis II comorbidity disorders in BD are difficult to interpret, with published studies reporting a wide prevalence range (9–89%), probably due to methodological differences. The most commonly comorbid personality disorders with BD belong to clusters B and C [172].

With respect to comorbidity patterns in relation to age, recently, our group carried out a study aimed to detect differences of psychiatric comorbidity between young, adult and senior patients with BD, finding a higher prevalence of anorexia and cannabis abuse in the younger group. Adult patients presented higher rates of OCD, anorexia and alcohol comorbidity, whereas senior patients presented more frequently benzodiazepines and alcohol abuse [173].

Possible determinants of psychopathological comorbidity and treatment issues Treating bipolar patients with psychiatric and medical comorbidity is particularly challenging because the treatment of psychiatric comorbidities in BD is not based on controlled data but, largely, on clinical experience [174].

The coexistence of an anxiety disorder, actually, may be additionally troublesome in the treatment of bipolar illness since antidepressants, the mainstay of pharmacologic treatment for anxiety, may adversely alter the course of BD. Identification of comorbid anxiety disorders in bipolar patients is therefore crucial. The treatment plan needs to balance the potential benefit/harm ratio of antidepressant administration. First-line pharmacological treatment of anxiety disorders are serotonergic antidepressants according to major treatment guidelines [175]. Nevertheless, the use of antidepressants may be problematic in bipolar illness [165, 176]. Specifically, antidepressants may induce manic episodes [177], destabilizing the illness over time by increasing the number of both manic and depressive episodes. There is evidence that the risk of these complications increases if bipolar patients receive antidepressants during periods of euthymia or in the long term [178] as

well as when they receive these compounds for the primary treatment of anxiety disorders. These potential antidepressant-related complications limit the use of these compounds for the treatment of anxiety disorders in bipolar patients, particularly in the treatment of comorbid OCD which may require full dosages of SRIs [179]. In some cases, however, the use of mood stabilizers as adjunctive agents for antidepressants could be useful. Recently, Holma and co-workers found that predictors of a switch from unipolar depression to BD included psychiatric comorbidity, in particular comorbid social phobia, OCD, and symptoms of cluster B personality disorder [180]. With respect to the comorbidity between BD and PD, the short-term efficacy of valproate has been recently reported in a follow-up study [181].

Other agents have shown some efficacy in the treatment of comorbid anxiety disorders in BD. These include the anticonvulsant gabapentin, for SP and PD [182, 183], and the second-generation antipsychotics olanzapine and quetiapine for PD, OCD, non-specific anxiety symptoms, and PTSD [184]. Lamotrigine was found to be superior to placebo in patients with BD and comorbid PTSD [185].

Combined treatment with quetiapine plus lithium or valproate was found to be more effective in maintaining euthymia over the long-term treatment of BD patients [186]. In addition, olanzapine and olanzapine-Fluoxetine combination showed a higher improvement in anxiety symptoms in BD patients [187]. Primary mood stabilizers may also have an effect but they have been less extensively studied [188]. While these agents are second-line choices for the treatment of anxious subjects without bipolar illness, they may be first-line agents in bipolar subjects.

With regard to comorbid SUD in BD, Nejtek and colleagues found that both quetiapine and risperidone reduced drug craving [189]. For comorbid conditions like migraine or substance abuse, valproate and other anticonvulsants are often the treatment of choice. Valproate proved to be superior to placebo in reducing interpersonal sensitivity, anger, and hostility in a sample of BD patients with comorbid borderline personality disorder [190]. Furthermore, valproate was more effective than placebo in reducing alcohol dependence [191]. Also topiramate was found to be effective in the treatment of BD with comorbid alcohol dependence compared with placebo [192].

When BD and eating disorders co-occur, it is necessary to select an agent effective in treating both syndromes and to pay attention to the potential risk to exacerbate one disorder with the treatment of the other. No randomized pharmacological trial is available in the management of comorbidity between BD and eating disorders. Olanzapine and risperidone have been reported to be effective in anorexia and in treatment-refractory eating disorders, showing positive results in the core symptoms of anorexia and BD [169]. Valproate was reported to be effective in ameliorating affective and bulimic symptoms in a case report [193]. On the other hand, valproate and atypical antipsychotics have been associated with an increase of binge eating in patients with BD.

In terms of comorbidity between BD and impulse control disorders, Hollander and colleagues examined the efficacy of lithium compared with placebo in a sample of BD patients with comorbid pathological gambling, finding a parallel improvement in both impulse control and mood symptoms in patients treated with sustained-release lithium [194].

As reported for SK, mood stabilizers, anticonvulsants, and antipsychotic medications have been linked to an increased risk for adverse metabolic changes in bipolar patients [195]. Therefore, in subjects at particular risk for these complications, it is important to consider the use of antipsychotics not associated with weight gain such as ziprasidone or aripiprazole [188, 196]. Adjunctive topiramate may be beneficial in controlling lithium-, valproate- or olanzapine-associated weight gain [197, 198].

Psychotic major depressive disorder (pMDD)

A large amount of recent data suggest that pMDD is different from non-psychotic depression in terms of biology, clinical symptoms, treatment response, and outcome. In view of such differences, some authors have argued that pMDD should be considered as a distinct diagnostic subtype of illness [199]. Patients with pMDD, in fact, often have longer duration of episodes, greater likelihood of recurrence, more residual symptoms, and slower time to recovery. Maj and collaborators [200] found that in pMDD patients, time to syndromal recovery from the index episode was longer and antipsychotics were more frequently used. Furthermore, the presence of delusions predicted a higher depressive morbidity during the prospective observation period and was associated with a more frequent family history of BD I [201]. An association between earlier age at onset at first hospitalization and increased comorbidity risk was also found in patients with pMDD [202].

Swartz and Shorter have outlined a different typology of psychotic depression: melancholic psychotic depression, psychosis-dominant depression, catatonic psychotic depression, psychotic-equivalent depression, tardive psychotic depression, drug-induced psychotic depression, and "coarse" brain disease psychotic depression [199].

Medical comorbidity

PMDD has been associated with a twofold increase in mortality in comparison to non-psychotic depression, with

deaths more frequently caused by comorbid chronic medical illness in a 15 year follow-up study [203]. Furthermore, comorbidity between pMDD and medical illness has been associated with a 50–75% increase in health service costs as reported in the US National Comorbidity survey [204]. This study showed that the presence of a comorbid medical disorder was associated with a greater likelihood of service utilization, and this observation has been replicated by Chisholm and colleagues [205].

Recently, Coryell and colleagues analyzed the relationship between HPA-axis hyperactivity, which characterizes many cases of severe depressive disorder, and mortality in a 17-year mortality follow-up study [206]. Older age and higher maximum post-dexamethasone cortisol concentrations predicted deaths due to cardiovascular disease. HPA-axis hyperactivity is probably one of the factors that links severe depressive disorders and cardiovascular mortality.

Psychopathological comorbidity

A study by Cassano and colleagues on a cohort of patients with affective disorders and psychotic symptoms found a higher prevalence of comorbid anxiety disorders (PD, OCD, SP) compared with the general population [202]. In particular, of the entire cohort, the 33.8% had a single anxiety disorder (23.4 of patients with pMDD), while 14.3% had 2 or 3 comorbid diagnoses. Patients with multiple anxiety comorbidity had significantly higher score on the Self-report Symptom Checklist (SCL-90) [207] and Brief Psychiatric Rating Scale (BPRS) [208] and a higher frequency of stimulant abuse. Interestingly, SP was more frequent in the unipolar than in the bipolar group.

A large study by Gaudiano and colleagues [209], involving 2,500 patients, found that the majority of pMDD patients exhibited more hallucinations than delusions, as well as higher rates of comorbid PTSD, OCD, and somatoform disorder, compared with non-psychotic depressed patients. PD and SUD were more frequent in pMDD, whereas GAD was found to be more common in non-psychotic depression. This study represents one of the most detailed examination of psychiatric comorbidity in pMDD, and it is consistent with prior reports [210–213].

Patients with pMDD were also found to be nearly 4 times more likely to have PTSD than non-psychotic depressed patients, suggesting that the presence of psychosis in outpatients with MDD could be associated with concurrent PTSD. Thus, the poorer longitudinal course of psychotic versus non-psychotic depression may also depend on the under-recognition of PTSD in psychotically depressed patients [214]. Recently, it has been suggested that pMDD with PTSD group tends to show greater severity and impairment compared with the groups with either pMDD only or having non-psychotic MDD plus PTSD. Furthermore, the pMDD with PTSD group had an earlier time to depressive onset, which appeared to contribute to the poorer outcome characteristic of this group. As such, it is important to consider both specific pharmacological and psychotherapeutic approaches for pMDD patients with PTSD comorbidity [215].

Cluster A personality disorders, particularly paranoid personality disorder, were found to be frequent in pMDD [209, 216], whereas Cluster B personality disorders (mainly histrionic personality disorder) were more common in non-psychotic patients [216].

The long-term course of pMDD was analyzed in a 10-year follow-up study at 6-month intervals for 5 years and then annually. This study found that pMDD patients had fewer weeks with minimal symptoms in each of the subsequent 10 years of follow-up but had more psychosocial impairment. Furthermore, psychotic features were found to be highly recurrent in patients with a lifetime illness of greater severity [217]. The chronology of the onset of the main and comorbid diagnoses in MPs has been studied by Strakowski and colleagues in 1995 [58]. Comorbidity was defined as antecedent if predated the age of onset of the psychotic disorder by more than 1 year. Comorbidity was present in 69% of the sample. Forty-nine percent of patients had multiple comorbid diagnoses. Comorbidity was antecedent to psychosis in over 80% of the patients. These antecedent comorbidities may represent either risk factors or prodromal syndromes for the psychotic disorder. Furthermore, both antecedent and overall comorbidity were more commonly associated with affective than with non-affective psychoses with significantly higher rates in pMDD than in SK. In particular, patients with pMDD presented the highest rates of comorbidity with alcohol abuse and antecedent PTSD. The main psychopathological comorbidity patterns in pMDD are summarized in Table 5.

Treatment issues in pMDD Several factors modify the outcome in severe depression including pre-treatment severity of illness, comorbidity with anxiety disorders, SUDs, personality disorders, and treatment modalities.

Antidepressant monotherapy may be effective against psychotic depression, but only about 1 out of 4 treated patients responds [218]. Atypical antipsychotic agents also may be effective as monotherapy. Actually, the recommended treatment for psychotic depression may be a combination of the 2, i.e., antidepressants plus antipsychotics. Augmentation with lithium or conventional antipsychotic drugs may also be useful in psychotic depression. Psychotic depression may be more likely to respond to electroconvulsive therapy than non-psychotic depression [199, 219].

Table 5 Epidemiological estimates of main comorbid psychopathological conditions in pMDD

Psychiatric disorders	References	Prevalence in pMDD	Prevalence in general population [225, 226]
Anxiety disorders (total)	Cassano et al. [202]	23.4% (cross-sectional)	12% (12 month)
GAD	Gaudiano et al. [209]	8.3% (lifetime)	1.7% (12 month)
OCD	Gaudiano et al. [209]	21.7% (lifetime)	0.7% (12 month)
PTSD	Gaudiano et al. [215]	56.7% (lifetime)	6.8% (lifetime)
	Zimmerman et al. [214]	57.9 (cross-sectional)	
PD	Gaudiano et al. [209]	43.3% (lifetime)	1.8% (12 month)
SP	Gaudiano et al. [209]	48.3% (lifetime)	2.3% (12 month)
Substance use disorders	Gaudiano et al. [209]	55.0% (lifetime)	20% (lifetime)
Impulse control disorders	Gaudiano et al. [209]	16.7% (lifetime)	5.2% (lifetime)
Somatoform disorders	Gaudiano et al. [209]	20% (lifetime)	6.3% (12 month)
Personality disorders	Gaudiano et al. [209]	17–32.4% (lifetime)	–
Eating disorders	Gaudiano et al. [209]	21.7% (lifetime)	0.4% (12 month)

The clinical and laboratory profile of pMDD suggests that treatment aimed at modifying the activity of the HPA axis might be effective. In particular, an intervention aimed to block low-affinity glucocorticoid receptors in the prefrontal cortex and hippocampus might improve both cognition and psychotic aspects of the disorder [220]. One candidate drug for this approach is mifepristone, an agent that was recently approved in the United States for the induction of abortions. In addition to its abortifacient properties, this compound is an antagonist of glucocorticoid receptors [221]. Other treatment approaches that might be helpful include the use of adjunctive psychotherapy or behavioral interventions given the high comorbidity with anxiety disorders [219].

Conclusions

Nosographic evolution of MPs currently separates these conditions into either psychotic (e.g., SK and Schizoaffective Disorder) and affective disorders (psychotic forms of BD and MDD). However, dimensional diagnostic models can approach MPs using a *continuum* model [222], which is based on genetic and neurobiological underpinnings. The presence of psychotic symptoms in these disorders represents a clinical unifying dimension. The high prevalence of comorbidity in MPs is partly a consequence of the current categorial nosographic systems. It represents a common clinical feature (i.e., psychosis) and potentially reflects the discrepancy between the pragmatic needs of classificatory systems and the way dysfunction in the brain is responsible for MPs to occur. The presence of comorbidity in MPs does not only consist of other psychiatric (co-)occurring disorders, but also of medical comorbid conditions. Taken as a whole, comorbid psychopathological and medical conditions complicate the diagnosis and worsen the outcome, increasing morbidity and mortality as well as functioning and quality of life. Despite the magnitude of the comorbidity phenomenon in MPs, it has only recently gained attention in clinical trials. In fact, treatment approaches for comorbid MPs have been less extensively investigated compared with non-comorbid cases. However, patients with comorbid MPs seem to be particularly difficult to treat. Pharmacological and psychotherapic treatments for these cases can only rarely rely on specific RCTs, and treatment guidelines need to be implemented in this specific area.

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References

1. Tamminga CA, Holcomb HH (2005) Phenotype of schizophrenia: a review and formulation. Mol Psychiatry 10(1):27–39
2. Burgy M (2008) The concept of psychosis: historical and phenomenological aspects. Schizophr Bull 34(6):1200–1210
3. Beer M (1996) Psychosis: a history of the concept. Compr Psychiatry 37:273–291
4. Hoenig J (1983) The concept of schizophrenia. Kraepelin-Bleuler-Schneider. Br J Psychiatry 142:547–556
5. Ghaemi SN (2009) Nosologomania: DSM & Karl Jaspers' critique of Kraepelin. Philos Ethics Humanit Med 4:10
6. Cassano GB, Pini S, Saettoni M, Rucci P, Dell'Osso L (1998) Occurrence and clinical correlates of psychiatric comorbidity in patients with psychotic disorders. J Clin Psychiatry 59(2):60–68
7. Amador XF, Strauss DH, Yale SA, Flaum MM, Endicott J, Gorman JM (1993) Assessment of insight in psychosis. Am J Psychiatry 150(6):873–879
8. Crow TJ (2007) How and why genetic linkage has not solved the problem of psychosis: review and hypothesis. Am J Psychiatry 164(1):13–21

9. Greene T (2007) The Kraepelinian dichotomy: the twin pillars crumbling? Hist Psychiatry 18(71):361–379
10. Angst J, Gamma A (2008) Diagnosis and course of affective psychoses: was Kraepelin right? Eur Arch Psychiatry Clin Neurosci 258(2):107–110
11. Crow TJ (1998) From Kraepelin to Kretschmer leavened by Schneider: the transition from categories of psychosis to dimensions of variation intrinsic to homo sapiens. Arch Gen Psychiatry 55(6):502–504
12. Craddock N, Forty L (2006) Genetics of affective (mood) disorders. Eur J Hum Genet 14(6):660–668
13. Blackwood DH, Pickard BJ, Thomson PA, Evans KL, Porteous DJ, Muir WJ (2007) Are some genetic risk factors common to schizophrenia, bipolar disorder and depression? Evidence from DISC1, GRIK4 and NRG1. Neurotox Res 11(1):73–83
14. Abdolmaleky HM, Zhou JR, Thiagalingam S, Smith CL (2008) Epigenetic and pharmacoepigenomic studies of major psychoses and potentials for therapeutics. Pharmacogenomics 9(12):1809–1823
15. Burmeister M, McInnis MG, Zöllner S (2008) Psychiatric genetics: progress amid controversy. Nat Rev Genet 9(7):527–540
16. Badcock C, Crespi B (2006) Imbalanced genomic imprinting in brain development: an evolutionary basis for the aetiology of autism. J Evol Biol 19(4):1007–1032
17. Crespi B, Stead P, Elliot M (2009) Evolution in health and medicine Sackler colloquium: comparative genomics of autism and schizophrenia. Proc Natl Acad Sci USA 107(1):1736–1741
18. Laursen TM, Agerbo E, Pedersen CB (2009) Bipolar disorder, schizoaffective disorder, and schizophrenia overlap: a new comorbidity index. J Clin Psychiatry 70(10):1432–1438
19. Grace AA (2006) Disruption of cortical-limbic interaction as a substrate for comorbidity. Neurotox Res 10(2):93–101
20. Van Snellenberg JX, De Candia T (2009) Meta-analytic evidence for familial coaggregation of SK and BD. Arch Gen Psychiatry 66(7):748–755
21. Berrettini W (2003) Evidence for shared susceptibility in bipolar disorder and schizophrenia. Am J Med Genet C Semin Med Genet 123C(1):59–64
22. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P, International Schizophrenia Consortium (2009) Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460(7256):748–752
23. Moskvina V, Craddock N, Holmans P, Nikolov I, Pahwa JS, Green E, WellcomeTrust Case Control Consortium, Owen MJ, O'Donovan MC (2009) Gene-wide analyses of genome-wide association data sets: evidence for multiple common risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk. Mol Psychiatry 14(3):252–260
24. Grozeva D, Kirov G, Ivanov D, Jones IR, Jones L, Green EK, St Clair DM, Young AH, Ferrier N, Farmer AE, McGuffin P, Holmans PA, Owen MJ, O'Donovan MC, Craddock N, Wellcome Trust Case Control Consortium (2010) Rare copy number variants: a point of rarity in genetic risk for bipolar disorder and schizophrenia. Arch Gen Psychiatry 67(4):318–327
25. Krishnan R (2005) Psychiatric and medical comorbidities of BD. Psychosom Med 67:1–8
26. McElroy SL, Altshuler LL, Suppes T, Keck PE Jr, Frye MA, Denicoff KD, Nolen WA, Kupka RW, Leverich GS, Rochussen JR, Rush AJ, Post RM (2001) Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with BD. Am J Psychiatry 158(3):420–426
27. First MB (2005) Clinical utility: a prerequisite for the adoption of a dimensional approach in DSM. J Abnorm Psychol 114(4):560–564
28. Cimpean D, Torrey WC, Green AI (2005) SK and co-occuring general medical illness. Psychiatry Ann 35:71–78
29. McGrath J, Saha S, Chant D, Welham J (2008) SK: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 30:67–76
30. Carney PC, Jones L, Woolson RF (2006) Medical comorbidity in women and men with SK. J Gen Intern Med 21:1133–1137
31. Lyketesos CG, Dunn G, KaminSky MJ, Breakey WR (2002) Medical comorbidity in psychiatric inpatients: relation to clinical outcomes and hospital length of stay. Psychosomatics 43:24–30
32. Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB (2007) Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and SK. J Clin Psychiatry 68(6):899–907
33. Saha S, Chant D, McGrath J (2007) A systematic review of mortality in SK: is the differential mortality gap worsening over time? Arch Gen Psychiatry 64(10):1123–1131
34. Ruetsch O, Viala A, Bardou H, Martin P, Vacheron MN (2005) Psychotropic drugs induced weight gain: a review of the literature concerning epidemiological data, mechanisms and management. Encephale 31(4 Pt 1):507–516
35. Baillargeon JG, Paar DP, Wu H, Giordano TP, Murray O, Raimer BG, Avery EN, Diamond PM, Pulvino JS (2008) Psychiatric disorders, HIV infection and HIV/hepatitis co-infection in the correctional setting. AIDS Care 20(1):124–129
36. Tang WK, Sun FC, Ungvari GS, O'Donnell D (2004) Oral health of psychiatric in-patients in Hong Kong. Int J Soc Psychiatry 50(2):186–191
37. Weber NS, Cowan DN, Millikan AM, Niebuhr DW (2009) Psychiatric and general medical conditions comorbid with schizophrenia in the national hospital discharge survey. Psychiatr Serv 60(8):1059–1067
38. Koponen H, Alar A, Saari K, Pelkonen O, Huikuri H, Raatikainen P, Savolainen M, Isohanni M (2008) SK and sudden cardiac death—a review. Nor J Psychiatry 62:342–345
39. Laursen TM, Munk-Olsen T, Agerbo E, Gasse C, Mortesen PB (2009) Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. Arch Gen Psychiatry 66(7):713–720
40. Bauer M, Goetz T, Glenn T, Whybrow PC (2008) The thyroid-brain interaction in thyroid disorders and mood disorders. J Neuroendocrinol 20(10):1101–1114
41. Monteleone P, Martiadis V, Maj M (2009) Management of schizophrenia with obesity, metabolic and endocrinological disorders. Psychiatr Clin North Am 32(4):775–794
42. Ryan MC, Collins P, Thakore JH (2003) Impaired fasting glucose tolerance in first-episode, drug-naive patients with SK. Am J Psychiatry 160(2):284–289
43. Meyer JM, Stahl SM (2009) The metabolic syndrome and schizophrenia. Acta Psychiatr Scand 119(1):4–14
44. Mitchell BD (2009) Clustering of SK with other comorbidities—what can we learn? Schizophr Bull 35(2):282–283
45. Yazıcı MK, Anıl Yağcıoğlu AE, Ertuğrul A, Eni N, Karahan S, Karaağaoğlu E, Tokgözoğlu SL (2010) The prevalence and clinical correlates of metabolic syndrome in patients with schizophrenia: findings from a cohort in Turkey. Eur Arch Psychiatry Clin Neurosci 261(1):69–78
46. Leucht S, Burkard T, Henderson J, Maj M, Sartorius N (2007) Physical illness and SK: a review of the literature. Acta Psychiatr Scand 116(5):317–333
47. O'Keane V (2008) Antipsychotic-induced hyperprolactinaemia, hypogonadism and osteoporosis in the treatment of SK. J Psychopharmacol 22(2):70–75
48. Watanabe Y, Nunokawa A, Kaneko N, Muratake T, Arinami T, Ujike H, Inada T, Iwata N, Kunugi H, Itokawa M, Otowa T,

Ozaki N, Someya T (2009) Two-stage case-control association study of polymorphisms in rheumatoid arthritis susceptibility genes with SK. J Hum Genet 54(1):62–65
49. Brown S, InSkip H, Barraclough B (2000) Causes of the excess mortality of schizophrenia. Br J Psychiatry 177:212–217
50. King-Hele S, Webb RT, Mortensen PB, Appleby L, Pickles A, Abel KM (2009) Risk of stillbirth and neonatal death linked with maternal mental illness: a national cohort study. Arch Dis Child Fetal Neonatal Ed 94(2):F105–F110
51. Newcomer JW (2009) Comparing the safety and efficacy of atypical antipsychotics in psychiatric patients with comorbid medical illnesses. J Clin Psychiatry 70(S3):30–36
52. Oud MJ, Meyboom-de Jong B (2009) Somatic diseases in patients with schizophrenia in general practice: their prevalence and health care. BMC Fam Pract 10:32
53. Kozumplik O, Uzun S, Jakovljević M (2009) Psychotic disorders and comorbidity: somatic illness vs. side effect. Psychiatr Danub 21(3):361–367
54. Sowden GL, Huffman JC (2009) The impact of mental illness on cardiac outcomes: a review for the cardiologist. Int J Cardiology 132:30–37
55. Riecher-Rössler A, Schmid C, Bleuer S, Birkhäuser M (2009) Antipsychotics and hyperprolactinaemia: pathophysiology, clinical relevance, diagnosis and therapy. Neuropsychiatr 23(2):71–83
56. Sachdev PS (2000) The current status of tardive dySkinesia. Aust N Z J Psychiatry 34(3):355–369
57. Altamura AC, Goikolea JM (2008) Differential diagnoses and management strategies in patients with SK and BD. Neuropsychiatr Dis Treat 4(1):311–317
58. StrakowSki SM, Keck PE, McElroy SL, Lonczak HS, West SA (1995) Chronology of comorbid and principal syndromes in first-episode psychosis. Compr Psychiatry 36(2):106–112
59. Buckley PF, Miller BJ, Lehrer DS, Castle DJ (2009) Psychiatric comorbidities and SK. Schizophr Bull 35(2):383–402
60. Cantor-Graae E, Nordstrom LG, McNeil TF (2001) Substance abuse in SK: a review of the literature and a study of correlates in Sweden. Schizophr Res 48:69–82
61. Green AI (2006) Treatment of SK and comorbid substance abuse: pharmacologic approaches. J Clin Psychiatry 67(7): 31–35
62. Volkow ND (2009) Substance use disorders in SK: clinical implications of comorbidity. Schizophr Bull 35:469–472
63. Fazel S, Gulati G, Linsell L, Geddes JR, Grann M (2009) Schizophrenia and violence: systematic review and meta-analysis. PLoS Med 6(8):e1000120
64. Schnell T, Neisius K, Daumann J, Gouzoulis-Mayfrank E (2010) Prevalence of psychosis/substance abuse comorbidity: clinical-epidemiological findings from different treatment settings in a large German city. Nervenarzt 81(3):323–328
65. Gross-Isseroff R, Hermesh H, Zohar J, Weizman A (2003) Neuroimaging communality between schizophrenia and obsessive compulsive disorder: a putative basis for schizo-obsessive disorder? World J Biol Psychiatry 4(3):129–134
66. Shioiri T, Shinada K, Kuwabara H, Someya T (2007) Early prodromal symptoms and diagnoses before first psychotic episode in 219 inpatients with schizophrenia. Psychiatry Clin Neurosci 61(4):348–354
67. Siris SG (2000) Depression in schizophrenia: perspective in the era of 'atypical' antipsychotic agents. Am J Psychiatry 157:1379–1389
68. An der Heiden W, Könnecke R, Maurer K, Ropeter D, Häfner H (2005) Depression in the long-term course of schizophrenia. Eur Arch Psychiatry Clin Neurosci 255:174–184
69. Birchwood M, Mason R, MacMillan F, Healy J (1993) Depression, demoralization and control over psychotic illness: a comparison of depressed and non-depressed patients with a chronic psychosis. Psychol Med 23(2):387–395
70. Tibbo P, Swainson J, Chue P, LeMelledo JM (2003) Prevalence and relationship to delusions and hallucinations of anxiety disorders in schizophrenia. Depress Anxiety 17(2):65–72
71. Goodman C, Finkel B, Naser M, Andreyev P, Segev Y, Kurs R, Melamed Y, Bleich A (2007) Neurocognitive deterioration in elderly chronic schizophrenia patients with and without PTSD. J Nerv Ment Dis 195(5):415–420
72. Cunill R, Castells X, Simeon D (2009) Relationships between obsessive-compulsive symptomatology and severity of psychosis in schizophrenia: a systematic review and meta-analysis. J Clin Psychiatry 70(1):70–82
73. PoyurovSky M, Glick I, Koran L (2008) Lamotrigine augmentation in schizophrenia and schizoaffective patients with obsessive-compulsive symptoms. J Psychopharmacol 24(6): 861–866
74. Mazeh D, Bodner E, Weizman R, Delayahu Y, Cholostoy A, Martin T, Barak Y (2009) Co-morbid social phobia in schizophrenia. Int J Soc Psychiatry 55(3):198–202
75. Henquet C, Di Forti M, Morrison P, Kuepper R, Murray RM (2008) Gene-environment interplay between cannabis and psychosis. Schizophr Bull 34(6):1111–1121
76. Rais M, Cahn W, Van Haren N, Schnack H, Caspers E, Hulshoff Pol H, Kahn R (2008) Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. Am J Psychiatry 165(4):490–496
77. Chambers RA, Krystal JH, Self DW (2001) A neurobiological basis for substance abuse comorbidity in schizophrenia. Biol Psychiatry 50(2):71–83
78. Bonta J, Law M, Hanson K (1998) The prediction of criminal and violent recidivism among mentally disordered offenders: a meta-analysis. Psychol Bull 123(2):123–142
79. Bartels SJ, Drake RE (1988) Depressive symptoms in schizophrenia: comprehensive differential diagnosis. Compr Psychiatry 29(5):467–483
80. Sim K, Mahendran R, Siris SG, Heckers S, Chong SA (2004) Subjective quality of life in first episode schizophrenia spectrum disorders with comorbid depression. Psychiatry Res 129(2): 141–147
81. Siris SG (1987) Akinesia and postpsychotic depression: a difficult differential diagnosis. J Clin Psychiatry 48(6):240–243
82. Weissman MM, Myers JK (1980) Clinical depression in alcoholism. Am J Psychiatry 137(3):372–373
83. Moller HJ (2005) Occurrence and treatment of depressive comorbidity/cosyndromality in schizophrenic psychoses: conceptual and treatment issues. World J Biol Psychiatry 6(4):247–263
84. Möller HJ (2007) Clinical evaluation of negative symptoms in schizophrenia. Eur Psychiatry 22(6):380–386
85. Loas G, Azi A, Noisette C, Legrand A, Yon V (2009) Fourteen-year prospective follow-up study of positive and negative symptoms in chronic schizophrenic patients dying from suicide compared to other causes of death. Psychopathology 42(3): 185–189
86. Siris SG (2001) Suicide and schizophrenia. J Psychopharmacol 15(2):127–135
87. Altamura AC (1996) Argomenti di clinica e farmacoterapia delle psicosi maggiori. Mc Graw-Hill, Milano
88. Altamura AC (1996) Novel antipsychotics and the problem of clinical stabilization in SK: are they "stabilizer" rather than typical compounds? Int Clin Psychopharmacol 11:153–155
89. Gründer G, Hippius H, Carlsson A (2009) The 'atypicality' of antipsychotics: a concept re-examined and re-defined. Nat Rev Drug Discov 8(3):197–202
90. Newcomer JW (2007) Antipsychotic medication: metabolic and cardiovascular risk. J Clin Psychiatry 68(4):8–13

91. Newcomer JW (2005) Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 19(1):1–93
92. Glick ID, PoyurovSky M, Ivanova O, Koran LM (2008) Aripiprazole in schizophrenia patients with comorbid obsessive-compulsive symptoms: an open-label study of 15 patients. J Clin Psychiatry 69(12):1856–1859
93. Diaz FJ, James D, Botts S, Maw L, Susce MT, de Leon J (2009) Tobacco smoking behaviors in BD: a comparison of the general population, SK, and major depression. Bipolar Disord 11(2): 154–165
94. Green AI, Salomon MS, Brenner MJ, Rawlins K (2002) Treatment of schizophrenia and comorbid substance use disorder. Curr Drug Targets CNS Neurol Disord 1(2):129–139
95. Jentsch JD, Roth RH, Taylor JR (2000) Role for dopamine in the behavioral functions of the prefrontal corticostriatal system: implications for mental disorders and psychotropic drug action. Prog Brain Res 126:433–453
96. Zullino DF, Waber L, Khazaal Y (2008) Cannabis and the course of SK. Am J Psychiatry 165(10):1357–1358
97. Wobrock T, Soyka T (2008) Pharmacotherapy of SK with comorbid substance use disorder—reviewing the evidence and clinical recommendations. Progr Neuropsychopharmacol Biolog Psychiatr 32:1375–1385
98. Roser P, Vollenweider FX, Kawohl W (2008) Potential antipsychotic properties of central cannabinoid (CB(1)) receptor antagonists. World J Biol Psychiatry 7:1–12
99. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders (text rev), 4th edn. American Psychiatric Association, Washington, DC
100. Falkai P, Wobrock T, Lieberman J, Glenthon JB, Gattaz WF, Moller HJ (2005) WFSBP task force on treatment guidelines for schizophrenia. World federation of societies of biological psychiatry (WFSBP) Guidelines for biological treatment of schizophrenia, part 1: acute treatment of schizophrenia. World J Biol Psychiatry 6(3):132–191
101. Altamura AC, Sassella F, Santini A, Montresor C, Fumagalli S, Mundo E (2003) Intramuscular preparations of antipsychotics: uses and relevance in clinical practice. Drugs 63(5):493–512
102. Altamura AC, Bobo WV, Meltzer HY (2007) Factors affecting outcome in SK and their relevant for psychopharmacological treatment. Int Clin Psychopharmacol 22:249–267
103. Saravane D, Feve B, Frances Y, Corruble E, Lancon C, Chanson P, Maison P, Terra JL, Azorin JM (2009) Drawing up guidelines for the attendance of physical health of patients with severe mental illness. Encephale 35(4):330–339
104. Bryant-Comstock L, Stender M, Devercelli G (2002) Health care utilization and costs among privately insured patients with bipolar I disorder. Bipolar Disord 4(6):398–405
105. Gardner HH, Kleinman NL, Brook RA, Rajagopalan K, Brizee TJ, Smeeding JE (2006) The economic impact of BD in an employed population from an employer perspective. J Clin Psychiatry 67:1209–1218
106. Centorrino F, Mark TL, Talamo A, Oh K, Chang J (2009) Health and economic burden of metabolic comorbidity among individuals with bipolar disorder. J Clin Psychopharmacol 29(6): 595–600
107. Fenn HH, Bauer MS, Alshuler L et al (2005) Medical comorbidity and health-related quality of life in BD across the adult age span. J Affect Disord 86:47–60
108. Carney CP, Jones LE (2006) Medical comorbidity in women and men with Bipolar Disord: a population-based controlled study. Psychosom Med 68:684–691
109. Arnold LM (2003) Gender differences in BD. Psychiatr Clin North Am 26:595–620
110. Beyer J, Kuchibhatla M, Gersing K, Krishnan KR (2005) Medical comorbidity in a bipolar outpatient clinical population. Neuropsychopharmacology 30(2):401–404
111. Soreca I, Fagiolini A, Frank E, Houck PR, Thompson W, Kupfer DJ (2008) Relationship of general medical burden, duration of illness and age in patients with bipolar I disorder. J Psychiatr Res 42(11):956–961
112. Van Winkel R, De Hert M, Van Eyck D, Hanssens L, Wampers M, Scheen A, PeuSkens J (2008) Prevalence of diabetes and the metabolic syndrome in a sample of patients with BD. Bipolar Disord 10:342–348
113. Kemp DE, Gao K, Ganocy SJ, Caldes E, Feldman K, Chan PK, Conroy C, Bilali S, Findling RL, Calabrese JR (2009) Medical and substance use comorbidity in BD. J Affect Disord 116(1–2):64–69
114. Angst F, Stassen HH, Clayton PJ, Angst J (2002) Mortality of patients with mood disorders: follow-up over 34–38 years. J Affect Disord 68(2–3):167–181
115. Kupfer DJ (2005) The increasing medical burden in BD. JAMA 293(20):2528–2530
116. McIntyre RS, SoczynSka JK, Beyer JL, Woldeyohannes HO, Law CW, Miranda A, KonarSki JZ, Kennedy SH (2007) Medical comorbidity in BD: re-prioritizing unmet needs. Curr Opin Psychiatry 20(4):406–416
117. McIntyre RS, KonarSki JZ, Misener VL, Kennedy SH (2005) BD and diabetes mellitus: epidemiology, etiology, and treatment implications. Ann Clin Psychiatry 17(2):83–93
118. Fasmer OB (2001) The prevalence of migraine in patients with bipolar and unipolar affective disorders. Cephalalgia 21:894–899
119. McIntyre RS, KonarSki JZ, Wilkins K et al (2006) The prevalence and impact of migraine headache in bipolar disorder: results from the Canadian community health survey. Headache 46:973–982
120. FiSk JD, Morehouse SA, Brown MG, Skedgel C, Murray TJ (1998) Hospital-based psychiatric service utilization and morbidity in multiple sclerosis. Can J Neurol Sci 25:230–235
121. Schiffer RB, Wineman NM, Weitkamp LR (1986) Association between bipolar affective disorder and multiple sclerosis. Am J Psychiatry 143:94–95
122. Pine DS, Douglas CJ, Charles E, Davies M, Kahn D (1995) Patients with multiple sclerosis presenting to psychiatric hospitals. J Clin Psychiatry 56:297–306
123. Salmaggi A, Eoli M, La Mantia L, Erbetta A (1995) Parallel fluctuations of psychiatric and neurological symptoms in a patient with multiple sclerosis and bipolar affective disorder. Ital J Neurol Sci 16:551–553
124. McElroy SL, Frye MA, Suppes T, Dhavale D, Keck PE, Leverich GS et al (2002) Correlates of overweight and obesity in 644 patients with bipolar disorder. J Clin Psychiatry 63:207–213
125. Fagiolini A, Frank E, Houck PR, Mallinger AG, Swartz HA, Buysse DJ, Ombao H, Kupfer DJ (2002) Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. J Clin Psychiatry 63:528–533
126. Fagiolini A, Frank E, Scott JA, Turkin S, Kupfer DJ (2005) Metabolic syndrome in BD: findings from the BD Center for Pennsylvanians. Bipolar Disord 7(5):424–430
127. Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E (2003) Obesity as a correlate of outcome in patients with Bipolar I disorder. Am J Psychiatry 160:112–117
128. McIntyre RS, Keck PE Jr (2006) Comorbidity in BD: clinical and research opportunities. Bipolar Disord 8(6):645–647
129. Fagiolini A, Chengappa KN, Soreca I, Chang J (2008) BD and the metabolic syndrome: causal factors, psychiatric outcomes and economic burden. CNS Drugs 22(8):655–669

130. Kessing LV, Nilsson FM (2003) Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. J Affect Disord 73: 261–269
131. Kessing LV, Andersen PK (2004) Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? J Neurol Neurosurg Psychiatry 75:1662–1666
132. BarChana M, Levav I, Lipshitz I et al (2008) Enhanced cancer risk among patients with bipolar disorder. J Affect Disord 108:43–48
133. Arnold LM, Hudson JI, Keck PE et al (2006) Comorbidity of fibromyalgia and psychiatric disorders. J Clin Psychiatry 67:1219–1225
134. Fagiolini A, Goracci A (2009) The effects of undertreated chronic medical illnesses in patients with severe mental disorders. J Clin Psychiatry 70(3):22–29
135. Soreca I, Frank E, Kupfer DJ (2009) The phenomenology of BD: what drives the high rate of medical burden and determines long-term prognosis? Depress Anxiety 26(1):73–82
136. Roshanaei-Moghaddam B, Katon W (2009) Premature mortality from general medical illnesses among persons with BD: a review. Psychiatr Serv 60(2):147–156
137. McIntyre RS (2009) Understanding needs, interactions, treatment, and expectations among individuals affected by BD or SK: the UNITE global survey. J Clin Psychiatry 70(3):5–11
138. Merikangas KR, AkiSkal HS, Angst J et al (2007) Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. Arch Gen Psychiatry 64(5):543–552
139. StrakowSki SM, Tohen M, Stoll AL, Faedda GL, Goodwin DC (1992) Comorbidity in mania at first hospitalization. Am J Psychiatry 149(4):554–556
140. Tohen M, Greenfield SF, Weiss RD, Zarate CA Jr, Vagge LM (1998) The effect of comorbid substance use disorders on the course of bipolar disorder: a review. Harv Rev Psychiatry 6(3):133–141
141. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK (1990) Comorbidity of mental disorders with alcohol and other drug abuse. Results from the epidemiologic catchment area (ECA) study. JAMA 264(19):2511–2518
142. Kessler RC, Stang P, Wittchen HU, Stein M, Walters EE (1999) Lifetime co-morbidities between social phobia and mood disorders in the US national comorbidity survey. Psychol Med 29(3):555–567
143. Kessler RC, Rubinow DR, Holmes C et al (1997) The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 27:1079–1089
144. Sareen J, Cox BJ, Afifi TO et al (2005) Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. Arch Gen Psychiatry 62:1249–1257
145. Rodriguez BF, Bruce SE, Pagano ME et al (2005) Relationships among psychosocial functioning, diagnostic comorbidity, and the recurrence of generalized anxiety disorder, panic disorder, and major depression. J Anxiety Disord 19:752–766
146. Boylan KR, Bieling PJ, Marriott M et al (2004) Impact of comorbid anxiety disorders on outcome in a cohort of patients with BD. J Clin Psychiatry 65:1106–1113
147. Chen YW, Dilsaver SC (1995) Comorbidity of panic disorder in bipolar illness: evidence from the epidemiologic catchment area survey. Am J Psychiatry 152:280–282
148. Doughty CJ, Wells JE, Joyce PR et al (2004) Bipolar-panic disorder comorbidity within BD families: a study of siblings. Bipolar Disord 6:245–252
149. MacKinnon DF, McMahon FJ, Simpson SG, McInnis MG, DePaulo JR (1997) Panic disorder with familial BD. Biol Psychiatry 42:90–95
150. MacKinnon DF, Xu J, McMahon FJ et al (1998) BD and panic disorder in families: an analysis of chromosome 18 data. Am J Psychiatry 155:829–831
151. MacKinnon DF, ZamoiSki R (2006) Panic comorbidity with bipolar disorder: what is the manic-panic connection? Bipolar Disord 8(6):648–664
152. Hawgood J, De Leo D (2008) Anxiety disorders and suicidal behaviour: an update. Curr Opin Psychiatry 21(1):51–64
153. Kilbane EJ, Gokbayrak NS, Galynker I, Cohen L, Tross S (2009) A review of panic and suicide in bipolar disorder: does comorbidity increase risk? J Affect Disord 115:1–10
154. Altamura AC, Dell'Osso B, Berlin HA, Buoli M, Bassetti R, Mundo E (2010) Duration of untreated illness and suicide in bipolar disorder: a naturalistic study. Eur Arch Psychiatry Clin Neurosci 260(5):385–391
155. Simon GE, Hunkeler E, Fireman B, Lee JY, Savarino J (2007) Risk of suicide attempt and suicide death in patients treated for bipolar disorder. Bipolar Disord 9:526–530
156. Coryell W, Endicott J, Andreasen N et al (1985) Bipolar I, bipolar II, and nonbipolar major depression among the relatives of affectively ill probands. Am J Psychiatry 142:817–821
157. StrakowSki SM, Sax KW, McElroy SL et al (1998) Course of psychiatric and substance abuse syndromes co-occurring with BD after a first psychiatric hospitalization. J Clin Psychiatry 59:465–471
158. Brown GR, McBride L, Bauer MS et al (2005) Impact of childhood abuse on the course of BD: a replication study in U.S. veterans. J Affect Disord 89:57–67
159. Kennedy BL, Dhaliwal N, Pedley L et al (2002) Post-traumatic stress disorder in subjects with SK and BD. J Ky Med Assoc 100:395–399
160. Pollack MH, Simon NM, Fagiolini A et al (2006) Persistent posttraumatic stress disorder following September 11 in patients with BD. J Clin Psychiatry 67:394–399
161. Otto MW, Perlman CA, Wernicke R et al (2004) Posttraumatic stress disorder in patients with bipolar disorder: a review of prevalence, correlates, and treatment strategies. Bipolar Disord 6:470–479
162. Baldassano CF, Marangell LB, Gyulai L et al (2005) Gender differences in BD: retrospective data from the first 500 STEP-BD participants. Bipolar Disord 7:465–470
163. Grant BF, Hasin DS, Blanco C et al (2005) The epidemiology of social anxiety disorder in the United States: results from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry 66:1351–1361
164. Sajatovic M, Blow FC, Ignacio RV (2006) Psychiatric comorbidity in older adults with bipolar disorder. Int J Geriatr Psychiatry 21:582–587
165. El-Mallakh RS, Hollifield M (2008) Comorbid anxiety in BD alters treatment and prognosis. Psychiatr Q 79:139–150
166. Lee HS, Kim S, Choi I, Lee KU (2008) Prevalence and risk factors associated with suicide ideation and attempts in korean college students. Psychiatry Investig 5(2):86–93
167. Dalton EJ, Cate-Carter TD, Mundo E, Parikh SV, Kennedy JL (2003) Suicide risk in bipolar patients: the role of co-morbid substance use disorders. Bipolar Disord 5(1):58–61
168. Gao K, Tolliver BK, Kemp DE, Verduin ML, Ganocy SJ, Bilali S et al (2008) Differential interactions between comorbid anxiety disorders and substance use disorder in rapid cycling bipolar I or II disorder. J Affect Disord 110(1–2):167–173
169. McElroy SL, Kotwal R, Keck PE Jr (2006) Comorbidity of eating disorders with BD and treatment implications. Bipolar Disord 8(6):686–695

170. Angst J (1998) The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 50(2–3):143–151
171. Lewinsohn PM, Shankman SA, Gau JM, Klein DN (2004) The prevalence and co-morbidity of subthreshold psychiatric conditions. Psychol Med 34(4):613–622
172. Kay JH, Altshuler LL, Ventura J, Mintz J (1999) Prevalence of axis II comorbidity in bipolar patients with and without alcohol use disorders. Ann Clin Psychiatry 11(4):187–195
173. Dell'Osso B, Buoli M, Bortolussi S, Camuri G, Vecchi V, Altamura AC (2010) Patterns of Axis I comorbidity in relation to age in patients with Bipolar Disorder: a cross-sectional analysis. J Affect Disord (in press)
174. Singh JB, Zarate CA (2006) Pharmacological treatment of psychiatric comorbidity in BD: a review of controlled trials. Bipolar Disord 8:696–709
175. Bandelow B, Zohar J, Hollander E, Kasper S, Möller HJ et al (2008) World federation of societies of biological psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders—first revision. World J Biol Psychiatry 9(4):248–312
176. Ghaemi SN, Hsu DJ, Soldani F et al (2003) Antidepressants in BD: the case for caution. Bipolar Disord 5(6):421–433
177. Mundo E, Cattaneo E, Russo M, Altamura AC (2006) Clinical variables related to antidepressant-induced mania in bipolar disorder. J Affect Disord 92(2–3):227–230
178. Altshuler LL, Post RM, Leverich GS, MikalauSkas K, Rosoff A, Ackerman L (1995) Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 152(8): 1130–1138
179. Dell'Osso B, Altamura AC, Mundo E, Marazziti D, Hollander E (2007) Diagnosis and treatment of obsessive-compulsive disorder and related disorders. Int J Clin Pract 61(1):98–104
180. Holma KM, Melartin TK, Holma IA, Isometsä ET (2008) Predictors for switch from unipolar major depressive disorder to BD type I or II: a 5-year prospective study. J Clin Psychiatry 69(8):1267–1275
181. Perugi G, Frare F, Toni C, Tusini G, Vannucchi G, AkiSkal HS (2010) Adjunctive valproate in panic disorder patients with comorbid bipolar disorder or otherwise resistant to standard antidepressants: a 3-year "open" follow-up study. Eur Arch Psychiatry Clin Neurosci 260(7):553–560
182. Pande AC, Davidson JR, Jefferson JW, Janney CA, Katzelnick DJ, Weisler RH, Greist JH, Sutherland SM (1999) Treatment of social phobia with gabapentin: a placebo-controlled study. J Clin Psychopharmacol 19(4):341–348
183. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G (2000) Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin bipolar disorder study group. Bipolar Disord 2(3):249–255
184. Hirschfeld RM, Weisler RH, Raines SR, Macfadden W, for the BOLDER Study Group (2006) Quetiapine in the treatment of anxiety in patients with bipolar I or II depression: a secondary analysis from a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 67(3):355–362
185. Hertzberg MA, Butterfield MI, Feldman ME (1999) A preliminary study of lamotrigine for the treatment of PTSD. Biol Psychiatry 45:1226–1229
186. Altamura AC, Mundo E, Dell'Osso B, Tacchini G, Buoli M, Calabrese JR (2008) Quetiapine and classical mood stabilizers in the long-term treatment of BD: a 4-year follow up naturalistic study. J Affect Disord 110(1–2):135–141
187. Tohen M, Calabrese J, Vieta E, Bowden C, Gonzalez-Pinto A, Lin D, Xu W, Corya S (2007) Effect of comorbid anxiety on treatment response in bipolar depression. J Affect Disord 4(1–3):137–146
188. Keck PE Jr, Versiani M, Potkin S, West SA, Giller E, Ice K, Ziprasidone in Mania Study Group (2003) Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. Am J Psychiatry 160(4):741–748
189. Nejtek VA, Avila M, Chen LA, ZielinSki T, Djokovic M, Podawiltz A, Kaiser K, Bae S, Rush AJ (2008) Do atypical antipsychotics effectively treat co-occurring BD and stimulant dependence? A randomized, double-blind trial. J Clin Psychiatry 69(8):1257–1266
190. Frankenburg FR, Zanarini MC (2002) Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. J Clin Psychiatry 63(5):442–446
191. Salloum IM, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, Thase ME (2005) Efficacy of valproate maintenance in patients with BD and alcoholism: a double-blind placebo-controlled study. Arch Gen Psychiatry 62(1):37–45
192. Johnson BA, Ait-Daoud N, Bowden CL et al (2003) Oral topiramate for treatment of alcohol dependence: a randomized controlled trial. Lancet 361:1677–1685
193. Herridge PL, Pope HG Jr (1985) Treatment of bulimia and rapid-cycling bipolar disorder with sodium valproate: a case report. J Clin Psychopharmacol 5(4):229–230
194. Hollander E, Pallanti S, Allen A, Sood E, Baldini Rossi N (2005) Does sustained release lithium reduce impulsive gambling and affective instability versus placebo in pathological gamblers with bipolar spectrum disorders? Am J Psychiatry 162:137–145
195. Newcomer JW (2006) Medical risk in patients with BD and SK. J Clin Psychiatry 67(9):25–30
196. Goodnick PJ, Jerry JM (2002) Aripiprazole: profile on efficacy and safety. Expert Opin Pharmacother 3(12):1773–1781
197. Vieta E, Sanchez-Moreno J, Goikolea J et al (2004) Effects on weight and outcome of long-term olanzapine-topiramate combination treatment in bipolar disorder. J Clin Psychopharmacol 24:374–378
198. Yatham LN, Kennedy SH, Schaffer A et al (2009) Canadian network for mood and anxiety treatments (CANMAT) and international society for bipolar disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord 11(3): 225–255
199. Swartz CM, Shorter E (2007) Psychotic depression. Cambridge University press, Cambridge
200. Maj M, Pirozzi R, Magliano L, Fiorillo A, Bartoli L (2007) Phenomenology and prognostic significance of delusions in major depressive disorder: a 10-years prospective follow-up study. J Clin Psychiatry 68(9):1411
201. Weissman MM, Prusoff BA, Merikangas KR (1984) Is delusional depression related to BD? Am J Psychiatry 141:892–893
202. Cassano GB, Pini S, Saettoni M, Dell'Osso L (1999) Multiple anxiety disorder comorbidity in patients with mood spectrum disorders with psychotic features. Am J Psychiatry 156(3):474–476
203. Vythilingam M, Chen J, Bremner JD, Mazure CM, MaciejewSki PK, Nelson JC (2003) Psychotic depression and mortality. Am J Psychiatry 160(3):574–576
204. Wu L, Kouzis A, Leaf P (1999) Influence of comorbid alcohol and psychiatric disorders on utilization of mental health services in the national co-morbidity survey. Am J Psychiatry 156:1230–1236
205. Chisholm D, Diehr P, Knapp M, Patrick D, Treglia M, Simon G (2003) LIDO group depression status, medical comorbidity and resource costs. Evidence from an international study of major

depression in primary care (LIDO). Br J Psychiatry 183:121–131
206. Coryell W, Fiedorowicz J, Zimmerman M, Young E (2008) HPA-axis hyperactivity and mortality in psychotic depressive disorder: preliminary findings. Psychoneuroendocrinology 33(5):654–658
207. Derogatis LR, Lipman RS, Covi L (1976) SCL-90: an outpatient psychiatric rating scale: preliminary report. In: Guy W (ed) ECDEU assessment manual for pychopharmacology. Revised 1976. DHEW Publication No. (ADM), pp 76–338
208. Overall JE, Gorham DR (1962) The brief psychiatric rating scale. Psycol Rep 10:799
209. Gaudiano BA, Dalrymple KL, Zimmerman M (2009) Prevalence and clinical characteristic of psychotic versus nonpsychotic major depression in a general psychiatric outpatients clinic. Depress Anxiety 26:54–64
210. Johnson J, Horwath E, Weissman MM (1991) The validity of major depression with psychotic features based on a community study. Arch Gen Psychiatry 48:1075–1081
211. Coryell W, Pfohl B, Zimmerman M (1984) The clinical and neuroendocrine features of psychotic depression. J Nerv Ment Dis 172:521–528
212. Lattuada E, Serretti A, Cusin C, Gasperini M, Smeraldi E (1999) Symptomatologic analysis of psychotic and non-psychotic depression. J Affect Disord 54:183–187
213. Charney DS, Nelson JC (1981) Delusional and nondelusional unipolar depression: further evidence for distinct subtypes. Am J Psychiatry 138:328–333
214. Zimmerman M, Mattia JI (1999) Psychotic subtyping of major depressive disorder and posttraumatic stress disorder. J Clin Psychiatry 60(5):311–314
215. Gaudiano BA, Zimmerman M (2010) Does comorbid posttraumatic stress disorder affect the severity and course of psychotic major depressive disorder? J Clin Psychiatry 71(4):442–450
216. Serretti A, Lattuada E, Cusin C, Gasperini M, Smeraldi E (1999) Clinical and demographic features of psychotic and nonpsychotic depression. Compr Psychiatry 40(5):358–362
217. Coryell W, Leon A, Winokur G, Endicott J, Keller M, AkiSkal H, Solomon D (1996) Importance of psychotic features to long-term course in major depressive disorder. Am J Psychiatry 153(4):483–489
218. Fleming SK, Blasey C, Schatzberg AF (2004) Neuropsychological correlates of psychotic features in major depressive disorders: a review and meta-analysis. J Psychiatr Res 38(1):27–35
219. Sonawalla SB, Fava M (2001) Severe depression is there a best approach? CNS Drugs 15(10):765–776
220. Kling MA, Coleman VH, Schulkin J (2009) Glucocorticoid inhibition in the treatment of depression: can we think outside the endocrine hypothalamus? Depress Anxiety 26(7):641–649
221. DeBattista C, Belanoff J, Glass S, Khan A, Horne RL, Blasey C, Carpenter LL, Alva G (2006) Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. Biol Psychiatry 60(12):1343–1349
222. Lawrie SM, Hall J, McIntosh AM, Owens DG, Johnstone EC (2010) The 'continuum of psychosis': scientifically unproven and clinically impractical. Br J Psychiatry 197:423–425
223. Fan AH, Hassell J (2008) Bipolar Disorder and comorbid personality psychopathology: a review of the literature. J Clin Psychiatry 69:1794–1803
224. Kasper DL, Braunwald E, Fauci AS, Huser SL, Longo DL, Jameson JL (2005) Harrison's principles of internal medicine, 16° edn. McGraw-Hill, Italy
225. Wittchen HU, Jacob F (2005) Size and burden of mental disorders in Europe—a critical review and appraisal of 27 studies. Eur Neuropsychopharmacol 15:35–376
226. Kessler RC, Berglund P, Demler O, Jin R, Merikangas K (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psyc 62:593–603